Remarks

Claims 47-72 are currently pending. Applicants acknowledge with appreciation that claims 53-57 would be allowable if re-written in independent form including all of the limitations of the base and any intervening claims. With this amendment, claims 52 and 65-72 have been cancelled without prejudice. Applicants reserve the right to pursue the subject matter of the cancelled claims in one or more related applications. Claims 53 and 54 have been amended to incorporate the proper dependency based on the cancellation of claim 52. New claims 73-79, which ultimately depend from claim 53, have been added. Exemplary support in the instant application for new claims 73-79 is summarized in the table below. Thus, the amendment is fully supported by the application as originally filed and, as such, does not constitute new matter Upon entry of this Amendment, claims 47-51, 53-64, and 73-79 will be pending.

Applicants request entry and consideration of the amendments and remarks into the record.

Claim No.	Support in US 2005/0025745
73	paragraph [0074]
74	paragraphs [0074]-[0076]; Examples 2-4
75	paragraphs [0023], [0064]-[0071]
76	paragraphs [0068]-[0071]
77	paragraphs [0068], [0076], [0089], [0125]; Example 3
78	paragraphs [0023], [0064]-[0071], [0076], [0089], [0125]; Example 3
79	paragraphs [0141]-[0144]

I. Priority

The Patent Office alleges that no English translation of Japanese Patent Application No. 2000-287688, filed September 12, 2000, has been submitted. Thus, the Patent Office has granted the instant application the priority date of U.S. Patent Application No. 09/816,391, of which the instant application is a Continuation. Applicants respectfully point out that a certified copy of Japanese Patent Application No. 2000-287688 was, indeed, submitted to the Patent Office on Feb. 6, 2007. This submission was acknowledged by the Patent Office in the Office Action

mailed on April 6, 2007. Given these facts, Applicants assert that the instant application is entitled to the priority date of Japanese Patent Application No. 2000-287688, *i.e.*, September 12, 2000.

II. The Rejections for Indefiniteness Should be Withdrawn

Claim 52 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Without acquiescing to the propriety of the rejection, claim 52 has been cancelled with this Amendment, thus obviating the Patent Office's rejection. As such, Applicants respectfully request that the rejection under 35 U.S.C. § 112, second paragraph, for indefiniteness, be withdrawn.

III. The Rejections for Obviousness Should be Withdrawn

Claims 47-51 and 58-64 are rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over Yazawa, *et al.* (Proceedings of the American Association for Cancer Research Annual Meeting , Vol. 40, pp. 88, 1999; "Yazawa") in view of Brown, *et al.* (US. Publication NO. 2003/0103952; "Brown"), and in further view of both Goshima, *et al.* (Biochimie, Vol. 72, pp. 207-214, 1990; "Goshima" and Claret, *et al.* (J. Mol. Biol. Vol. 273, pp. 93-104, 1997; "Claret"). For at least the following reasons, Applicants respectfully disagree with this rejection.

A. The Legal Standard

A finding of obviousness requires that "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. §103(a).

In *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 USPQ2d 1385 (2007), the Supreme Court stated that the following factors set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966) still control an obviousness inquiry: (1) the scope and content of the prior art; (2) the differences between the prior art and the claimed invention; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *KSR*, 127 S.Ct. at 1734, 82 USPQ2d at 1388 quoting *Graham*, 383 U.S. at 17-18, 14 USPQ at 467. The Supreme Court

affirmed that to find obviousness, it is "*important to identify a reason* that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR*, 127 S.Ct. at 1741, 82 USPQ2d at 1396, emphasis added. Moreover, the relevant inquiry is whether the prior art suggests the invention and whether the prior art provides one of ordinary skill in the art with a reasonable expectation of success. *In re O'Farrell*, 853 F.2d 894 (Fed. Cir. 1988).

In *Takeda Chemical Ind., Ltd. v. Alphapharm Pty., Ltd.*, 429 F.3d (Fed. Cir. 2007), the Federal Circuit held that the compounds at issue were not *prima facie* obvious over a structurally similar compound because the prior art provided no motivation to make the specific change in structure.

Finally, in making a determination of obviousness, one must consider the prior art from the perspective of a person having ordinary skill in the art at the time the invention was made. "Measuring a claimed invention against the standard established by section 103 requires the oft-difficult but critical step of casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field." *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999), citing to *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983). The *KSR* Court, citing *Graham*, upheld the principle of *avoiding hindsight bias* and cautioned courts to *guard against reading into the prior art the teachings of the invention in issue*. 127 S.Ct. at 1742, 82 USPQ at 1397:

> A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning. See *Graham*, 383 U.S., at 36, 86 S.Ct. 684 (warning against a "temptation to read into the prior art the teachings of the invention in issue" and instructing courts to "'guard against slipping into the use of hindsight'" (quoting *Monroe Auto Equipment Co. v. Heckethorn Mfg. & Supply Co.*, 332 F.2d 406, 412 (C.A.6 1964))).

B. Yazawa, Either Alone or Combined with Brown, Goshima, or Claret Fails to Teach or Suggest the Claimed Invention

The Patent Office acknowledges that neither Yazawa nor Brown teach using an HU promoter in *Bifidobacterium* to express anti-tumor genes (*see* Office Action mailed August 21,

2008, page 6; "Office Action"). The Patent Office erroneously contends, however, that Goshima and Claret supply this deficiency of Yazawa and Brown.

As discussed below, Goshima concludes that the HU-like protein from *Bifidobacterium* exists mainly in a single, homodimeric form. Goshima is silent regarding possible *Bifidobacterium* HU-like protein promoter structure, possible regulation of HU-like protein expression, or how relatively strong or weak an HU-like protein promoter might be. In view of this lack of information in Goshima, despite its statement that *B. longum* "has received much attention in the fields of food industry and medical sciences[,]" (*see* Goshima, page 207, left column) nothing in Goshima teaches or suggests that an HU-like promoter should be used in vectors such as those recited in the pending claims, nor does Goshima provide any motivation to specifically modify particular vectors or *Bifidobacterium* compositions to yield either the specific vectors or bacteria recited in the pending claims. Thus, combining Goshima with Yazawa and Brown fails to render the pending claims obvious.

As also discussed below, even the addition of Claret to the Yazawa, Brown, and Goshima combination fails to render the pending claims obvious. At the outset, Applicants note that the Patent Office consistently refers to "the HU promoter" in the instant Office Action. For example, in discussing Claret, the Patent Office states that "the HU promoter was known in the art as a promoter which highly expresses HU protein in *E. coli* during logarithmic growth phase" (*see* Office Action, page 6). However, as discussed below, this in no way reflects the state of the art at the time the instant application was first filed. Rather, as reflected in Claret, at the time the instant application was first filed it was known that multiple *E. coli* forms of HU proteins existed, as did multiple *E. coli* HU promoters. Moreover, it was also appreciated that the multiple *E. coli* HU promoters – none of which are characterized by the cited art as strong promoters – are regulated in a complex manner, likely to assure that particular forms of the different *E. coli* HU proteins are produced at particular points during the *E. coli* growth cycle.

Given the single form HU-like protein system of *Bifidobacterium* versus the multiple form HU protein system of *E. coli*, coupled with the likely accompanying differences in regulatory requirements necessitated by such systems, one of ordinary skill in the art would not be able to reasonably predict which, if any, of the regulatory or structural features of the *E. coli* HU promoters might have parallels in the *Bifidobacterium* HU-like system. As such, the

disclosure of Claret fails to remedy the deficiencies of either Goshima or the combination of Yazawa, Brown, and Goshima.

1. Goshima

Goshima allegedly identifies the existence and purification of a HU-like protein in *B. longum*, referred to in the reference as HB1. Goshima analyzes this protein and determines that it likely exists mainly in a single form as a homotypic dimer. However, Goshima fails to provide any disclosure of the genetic location of the HB1 sequence in the *B. longum* genome nor does Goshima provide any disclosure whatsoever of the promoter(s) that regulate the sequence encoding HB1, or how HB1 protein expression might be regulated. Moreover, Goshima does not teach or suggest that HB1 is highly expressed in *Bifidobacterium* relative to other *Bifidobacterium* proteins, nor does Goshima address the strength of the HB1 promoter(s) or any potentially advantageous properties the HB1 promoter(s) might have.

The Patent Office contends that a motivating factor for one of ordinary skill in the art to use an HU promoter in accordance with the methods of the instantly claimed invention is that Goshima "suggest[s] *B. longum* could be used in the medical sciences" (*see* Office Action, page 8). Applicants respectfully point out that what Goshima actually states is that "*B. longum* is a major component of human intestinal flora and has received much attention in the fields of food industry and medical sciences" (*see* Goshima, page 9, left column). Moreover, Goshima provides no guidance whatsoever as to how their putative discovery of an HU-like protein in *B. longum* could contribute to *B. longum's* medical use. Thus, Applicants assert that because Goshima does not identify the HB1 promoter(s) and fails to discuss any potential use of the HB1 promoter, one of ordinary skill in the art would *not* conclude that the *Bifidobacterium* HU promoter should be used as a means to express a protein of interest in *Bifidobacterium*, let alone should be used in conjunction with the particular vectors or bacteria recited in the pending claims. Moreover, even taking into account the combined disclosure of Yazawa and Brown, the complete silence in Goshima regarding possible HU-like protein promoter structure or structures, promoter regulation, or promoter strength would also fail to provide adequate motivation to specifically modify vectors or bacteria to yield either the vectors or bacteria recited in the pending claims *See, Takeda Chemical Ind., Ltd. v. Alphapharm Pty., Ltd., supra.*

2. Claret

In contrast to Goshima's conclusions regarding *B. longum* HU-like protein, Claret reports that multiple different forms of the *E. coli* HU protein can exist. In particular, Claret states that the *E. coli* HU protein can comprise two distinct protein subunits (*i.e.*, HUα and HUβ) encoded by two different genes (*i.e.*, *hupA* and *hupB*) and, as such, that the *E. coli* HU protein can exist in three separate forms, *i.e.*, HUα homodimer, HUβ homodimer, and HUα/HUβ heterodimer. Claret further reports that expression of the *E. coli* HU protein subunits from *hupA* and *hupB* is complex, requiring *four* separate promoters (*i.e.*, *hupA* promoter, *hupB*-P2, *hupB*-P3, and *hupB*-P4). Claret investigates the complex interactions between the multiple HU promoters of *E. coli* and how transcription of the two *hup* genes of *E. coli* varies with the growth phase of *E. coli* (*see* Claret at page 100, right column), identifying a cascade of promoter activation throughout the growth phase of *E. coli*, the regulatory mechanisms of which were unknown to Claret (*see* Claret at page 101, left column). Indeed, Claret teaches that only *two of the four* HU promoters, *i.e.*, the *hupA* promoter and *hupB*-P2, are active during logarithmic phase (*see* Abstract of Claret and Claret at page 94), whereas the other two HU promoters are active at other times during the *E. coli* growth phase.

Contrary to the Patent Office's contention, Claret does not posit that the *E. coli* HU promoter plays the singular role of highly expressing HU protein during logarithmic growth. Rather, Claret identifies different activities of the four separate HU promoters and when each promoter is active during the *E. coli* growth cycle. Moreover, Claret does not teach or suggest that any of the *E. coli* HU promoters -- including the two promoters active during logarithmic growth -- analyzed are "strong" promoters relative to any other *E. coli* promoters nor does Claret teach or suggest that any of the *E. coli* HU promoters would be useful for expressing proteins other than HU.

3. The HU promoter was a non-obvious selection

As discussed, *supra,* Goshima does not identify the *Bifidobacterium* HU-like protein promoter, its regulation, or its strength. Nor does Goshima address the possibility that, like in *E. coli*, multiple *Bifidobacterium* HU-like protein promoters might exist. In fact, Goshima neglects to discuss the promoter(s) of this protein entirely. Thus, Applicants assert that even if one of

ordinary skill in the art applied the teaching of Goshima to Claret, they would have had no reasonable expectation of successfully isolating a *Bifidobacterium* HU promoter that could be used to highly express a desired protein. This is at least because Goshima: (i) reports that the HU-like protein in *B. longum* differs structurally from the *E. coli* HU proteins; and (ii) is completely silent with respect to the *Bifidobacterium* HU-like protein promoter(s); whereas Claret (i) reports that transcription of the *E. coli* HU protein is extremely complex, requiring multiple promoters with varying activities; (ii) does not report that any of the *E. coli* HU promoters are particularly strong relative to each other or to other *E. coli* promoters; and (iii) does not report or suggest that any of the *E. coli* HU promoters can be used to express proteins other than HU. Clearly, there is no nexus between Goshima and Claret, and thus, no reason why one of ordinary skill in the art would have applied Claret to Goshima in a manner that, together with Yazawa and Brown, would yield or suggest the instantly claimed invention.

Moreover, Applicants point out that at the time the invention was first filed, none of the *E. coli* HU promoters had been used for the expression of proteins that do not include an HU protein in any bacteria. Further, those of ordinary skill in the art, aware of the existence of HU promoters, repeatedly chose to utilize promoters *other than* those of HU to express bacterial proteins. Indeed, although it was known that an HU promoter existed in *Clostridium* (*see, e.g.*, Goshima at page 207, left column), even Brown elected to use promoters other than HU (Brown uses three separate promoters, the *E. coli* trpE promoter, the ferredoxin gene promoter, and the promoter/operator region of the *E. coli* lac operon, but does not use or contemplate the use of the *Clostridium* HU promoter whatsoever). Finally, Applicants note that although Goshima identified a potential HU-like protein in *Bifidobacterium* in 1990, it was not until the instant invention was first filed -- *ten years after Goshima's publication* -- that use of an HU-like promoter in a vector for protein expression in *Bifidobacterium* was undertaken. Rather, Applicants assert that it is only via hindsight analysis that the Patent Office can reach the conclusion that one of ordinary skill in the art would have been motivated, based on the disclosures of Goshima and Claret, to make the specific modifications to Yazawa and Brown to yield the vectors and cells recited in the pending claims. However, such analysis, of course, is inappropriate. *See In re Dembiczak* and *KSR International Co. v. Teleflex Inc, supra.*

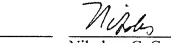
For at least the foregoing reasons, Applicants respectfully request that the rejection of the claims under 35 U.S.C. § 103(a), for obviousness, be withdrawn.

Conclusion

Applicants respectfully request entry and consideration of the foregoing amendments and remarks. No new matter has been introduced. The claims are believed to be free of the art and patentable. Withdrawal of the rejections and an allowance are earnestly sought.

Respectfully submitted,

Date: December 22, 2008



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